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BPAP is an effective second line therapy for obese patients with OSA failing regular CPAP: A prospective observational cohort study

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SUMMARY AT A GLANCE

There is a lack of effective alternative treatments for patients with OSA who do not tolerate CPAP therapy. We set out to investigate whether BPAP could be an effective second line therapy in this cohort of patients. We found that BPAP significantly improved adherence and symptom control when compared to CPAP.

Abstract

Background and objective: Continuous positive airway pressure (CPAP) is the commonest treatment for obstructive sleep apnoea (OSA), but many patients fail long-term therapy. Bilevel positive airway pressure (BPAP) is a potential alternative. We hypothesised that BPAP could improve treatment adherence and outcomes in patients who cannot tolerate CPAP.

Methods: Patients with OSA who failed CPAP (usage<4hours/day) and were referred to a tertiary sleep centre between 2014-2017 for BPAP were included. Age, gender, body-mass-index (BMI), co-morbidities, CPAP use and reasons for failure, Epworth Sleepiness Score (ESS), sleep study data, spirometry data and average maximum nightly compliance were recorded.

Results: 52 patients with OSA requiring CPAP>15cmH_20 (71% male, age 58 (15) years, BMI 42.6 (10.1) kg/m^2, AHI 51.1 (30.4)/hour) were studied; 62% had respiratory co-morbidities affecting nocturnal breathing including obesity hypoventilation syndrome and COPD; 25% had neuromuscular conditions and 17% had cardiovascular disease. CPAP was used for 199 (106-477) days prior to referral for BPAP. Reasons for CPAP failure were intolerant pressures (23%), uncontrolled symptoms (23%), mask problems (21%), adverse effects (13%), claustrophobia (8%), co-morbidities (8%), and other issues (4%). Lower expiratory positive airway pressures were needed with BPAP compared to CPAP (10 (8-12) vs 16.8 (15.7-19.2) cmH_20, p=0.001); patients achieved better adherence to BPAP (7.0 (4.0-8.5) vs 2.5 (1.6-6.7) hours/night, p=0.028) and better symptom control (ESS 4.0 (1.0-7.0) vs 10.0 (6.0-17.0) points, p=0.039).

Conclusion: In patients with moderate-severe OSA who fail CPAP therapy due to low adherence, BPAP is well tolerated and achieves sufficient control of sleep-disordered breathing and its symptoms.

Registration (local governance board): GSTT/2017/6977

Short title: BPAP for obese patients with OSA

Key words

1) Continuous positive airway pressure
2) Bilevel positive airway pressure
3) Obesity
4) Obstructive sleep apnea
5) Sleep medicine

Introduction

Obstructive sleep apnoea (OSA) is common [1] and its prevalence is rising due to the obesity pandemic. [2] OSA is characterised by repetitive occlusion of the upper airway during sleep leading to increased inspiratory effort, intermittent hypoxia and eventually arousal from sleep [3],[4] leading to excessive daytime sleepiness, increased cardiovascular risks and adverse health outcomes. [5]

The standard treatment for moderate-severe OSA is continuous positive airway pressure (CPAP). [6] CPAP requires patients to permanently sleep with a facial mask and long-term adherence is limited. [7] Various factors may contribute to sub-optimal long-term adherence, including a lack of symptom control and perceived benefit, claustrophobia, individual health-beliefs, pressure sores, air leak, adverse effects and sleep disturbance of bed partner to name a few. [8]

Alternative treatments to CPAP therapy include conventional advice about sleep hygiene, weight loss and posture. Therapeutic alternatives might include mandibular advancement devices, otolaryngology (ENT) and maxillo-facial surgery, [9] and, in experimental/audit settings, hypoglossal nerve stimulation [10] and transcutaneous electrical stimulation of the upper airway dilator muscles. [4],[11] Evidence-based practice is currently developing and specialist treatment should include assessment and guidance of suitable patients through an established treatment algorithm [12] to select the best second line therapy if CPAP is not tolerated.

Obese patients with OSA represent the typical phenotype in sleep clinics. [2],[5] They potentially require relatively high CPAP pressures [13],[14],[15] as obesity increases the load on the respiratory system. [13],[16] High CPAP pressures and subsequent increased air leak are likely to contribute to limited long-term adherence. An alternative to CPAP therapy is bilevel positive airway pressure

(BPAP); however, BPAP is frequently overlooked as it employs similar features to CPAP including a facial mask and positive pressures for ventilation. Furthermore, BPAP set up and maintenance requires adjustment of more variables and is more expensive than CPAP. [17] However, patients with severe OSA requiring high pressures on CPAP empirically find BPAP a more physiological breathing pattern and, thus, easier to tolerate.

We sought to review patients with OSA who had low CPAP adherence and high-pressure requirements. We hypothesised that those who do not tolerate standard CPAP therapy might better tolerate BPAP use over a sustained period.

Methods

This was an observational prospective cohort study of patients with OSA referred to a specialist tertiary sleep centre (Sleep Disorders Centre and Lane Fox Respiratory Unit at Guy's and St Thomas' NHS Foundation, London, UK). Patients unable to tolerate CPAP therapy despite the use of the latest technology, equipment (including nasal decongestants, humidifiers, skin protectors and a variety of mask types and sizes) and behavioural interventions were subsequently assessed for BPAP treatment (between 2014-2017). The study was registered as a service review (local clinical governance approval board reference number: GSTT/2017/6977) and patients provided informed verbal consent. The terminology used in this paper is in keeping with the recommendations of the American Academy of Sleep Medicine. [18]

The primary outcome of this observational and prospective cohort study was nightly adherence to treatment (BPAP vs CPAP), patients were their own controls (1^{st} CPAP vs 2^{nd} BPAP). Secondary outcomes were symptoms (Epworth Sleepiness Scale) and nocturnal respiratory control of OSA on the device.

Inclusion criteria

Patients with a diagnosis of OSA (Apnoea-Hypopnoea Index, AHI >5/hour, and/or 4% Oxygen Desaturation Index, ODI >5/hour), age 18-85 years, both genders, respiratory control of OSA with CPAP/BPAP during titration night, initial CPAP level >15cmH_2O and limited adherence (<4hours usage/night) after 3-months or intolerance of CPAP were included.

Exclusion criteria

Patients with no formal diagnosis of sleep disordered breathing, no previous CPAP therapy, CPAP<15cmH_2O, acute critical illness or acute comorbidity and an acceptable CPAP adherence were excluded.

All patients were clinically reviewed by a respiratory consultant and prospectively included; for data collection the "Electronic Patient Record" system was used to obtain age (years), body mass index (BMI, kg/m^2; measured prior to commencing CPAP), past medical history, oxygenation on room air while awake (SpO_2, %), spirometry (FEV_1 and FVC, L), AHI (h^{-1}) and/or 4% ODI (h^{-1}), duration of CPAP use (days/years), Epworth Sleepiness scale (ESS, points), reason for low CPAP adherence, bilevel positive airway pressure (BPAP) settings (inspiratory positive airway pressure, IPAP, and expiratory positive airway pressure, EPAP, cmH_2O; inspiratory time, Ti (s);

breaths per minute, BPM, min^{-1}), Adherence to CPAP and BPAP therapy, respectively (hours/night); the most recent data on record was used for the BPAP settings.

Patients had an initial diagnostic sleep study to establish the diagnosis (1st sleep study). This was followed by a CPAP titration night, during which respiratory control was established (2nd sleep study). Once the decision was taken that CPAP adherence was suboptimal and patients agreed to trial BPAP, there was another titration night (3rd sleep study). Prior to therapy the ESS, ODI, SpO_2, FEV_1, FVC and AHI were measured during respiratory polygraphy which included a combined SpO_2/tCO_2 monitor (TOSCA-Linde Medical System, Basel, Switzerland). These measurements were repeated at follow up appointments following initiation of each therapy. Therapy was set up in accordance with the titration protocols for BPAP, as previously described [19].

Sample Size Calculation

Based on previously published data from our Sleep Centre on CPAP compliance and adherence, [20] the provided parameters were a significance level (adjusted for sidedness) of 0.025, standard deviation within patients of 2.4 hours/day. The power expected was 0.85, and the expected minimally clinically important difference in the means of nightly adherence between the different treatment modalities was 1.5 hours. A total of 48 patients needed to enter this two-treatment crossover study to achieve a probability of 85% that the study would detect a difference at a two-sided 0.05 significance level, if the true difference between treatments was at least 1.5 hours/night. This was based on the assumption that the within-patient standard deviation of the response variable is 2.4 hours/night.

Statistical analysis

All data were collected using MS Excel 2016 (Microsoft, Seattle, WA/USA) and analysed with SPSS statistical analysis program V25 (IBM, New York, NY/USA). Following testing for normality (Shapiro-Wilk test) normally distributed data were presented as mean (±standard deviation), and non-normally distributed data as median (interquartile range: 1^{st} – 3^{rd} Quartile). For normally distributed data, means were compared using the students t-test and for non-normally distributed data the Wilcoxon Rank test was used. Fisher's exact test was performed to test for the equality of proportions to compare adequate adherence to therapy (>4 hours/night) among patients. For all tests, a level of significance was defined as $p \leq 0.05$.

Results

Patient characteristics

252 patients presented to the CPAP failure clinic between 2014-2017, of them 52 met the inclusion criteria for this cohort study. They were predominantly male, obese and middle-aged patients (71% male, 58(15)years, BMI 42.6(10.1)kg/m^2) with severe OSA (AHI 51.1(30.4)h^{-1}). The most common comorbidities were type 2 diabetes mellitus, hypertension and respiratory conditions such as COPD, asthma and chronic hypercapnic respiratory failure (Table 1). However, there was no significant airway obstruction when this group presented, neither when CPAP was initiated (FEV1 2.4(1.0)L; FVC 2.9(2.5-3.0)L) nor when BPAP was commenced (FEV1 2.1(1.1)L; FVC 2.5(1.8-3.4)L; p=0.374 and p=0.086, respectively). Daytime oxygenation

was within normal range (SpO_2 95.0(93.0-97.0) prior to CPAP *vs* 96.0(95.0-98.0)% prior to BPAP; p=0.084). Most patients had moderate-severe OSA (48%), 23% had combined OSA-Obesity Hypoventilation Syndrome (OHS), 10% had OSA-COPD overlap syndrome, 10% had an overlap of OSA-OHS-COPD, 8% had mixed sleep apnoea and 2% were diagnosed with mild OSA only. The identified patients with OHS had particularly elevated CO_2 levels while asleep, whereas, the daytime blood gas analysis of the cohort revealed marginally elevated levels and indicated compensated chronic abnormalities; while awake these patients had only mildly low pO2 9.3(1.5)kPa, borderline to normal pCO2 6.0(0.7)kPa and slightly elevated bicarbonate levels at 26.9(2.9)mmol/L, with a neutral pH 7.4(0.0).

CPAP therapy

Patients had been on CPAP therapy of 16.8(15.7-19.2)cmH_20 for 199(106-477)days prior to BPAP setup and the median usage of CPAP was 2.5(1.6-6.7)hours/night. The BPAP settings used included an inspiratory positive airway pressure (IPAP) of 21(5)cmH_2O, an expiratory positive airway pressure (EPAP) of 10(8-12)cmH_2O, inspiratory time (Ti) was 1.2(1.2-1.4)s and the backup rate (BUR) was 14(10-14)min^{-1}. Reasons for limited CPAP usage were high pressures, uncontrolled symptoms, mask problems and other adverse effects of the treatment (Table 2). The main issues with the mask included general discomfort (69%), leaking (15%), trouble with the fit (8%) and difficulty wearing the mask while sleeping prone (8%). Adverse effects experienced by patients on CPAP therapy were dry mouth (30%), headaches (14%), nausea (14%), aerophagy (14%), skin sores/infection (14%) and nasal congestion (14%); memory problems and the need for other clinical interventions were less common causes.

Ten patients reported interface related difficulties when using BPAP, six had suboptimal adherence. Reasons for suboptimal adherence were mask leak (n=3), claustrophobia (n=2) and waking at night feeling breathless (n=1). The other four patients reported a dry throat, uncomfortable mask straps, mask leak and disturbance of their partners.

CPAP vs BPAP therapy

The baseline AHI was 51.1(30.4)h^{-1} and the 4%ODI was 53.5(37.6)h^{-1}. During the 1st titration night on CPAP therapy the AHI was 26.2(19.0)h^{-1} (p=0.008) and the 4%ODI was 21.9(19.7) h^{-1} (p=0.02). Compared to CPAP the titration night using BPAP resulted in a similar reduction of the 4%ODI (25.2(24.5)h^{-1}; p=0.75). Once patients were established on the respective domiciliary treatment, both CPAP and BPAP controlled OSA and reduced the ODI to <5/hour for at least the last hour during the titration night.

Adherence to CPAP and BPAP therapy was significantly different at 6-weeks follow up (2.5(1.6-6.7) on CPAP *vs* 7.0(4.0-8.5)hours/night on BPAP (p=0.028)). 75.7% of patients achieved an adequate nightly adherence (adherence>4 hours/night) using BPAP compared to 42.9% of patients using CPAP therapy (p=0.045). Both therapies improved subjective sleepiness measures. The baseline ESS (16.0(8.0-19.0)points) dropped significantly more with BPAP usage than with CPAP (ESS on CPAP 10.0(6.0-17.0) *vs* BPAP 4.0(1.0-7.0)points; p=0.039). On BPAP, patients required a lower EPAP compared to the previously used CPAP levels (10(8-12)cmH_20 *vs* 16.8(15.7-19.2)cmH_20; p=0.001) to maintain sufficient control of OSA.

Discussion

For symptomatic patients with severe OSA, who have low adherence or tolerance of CPAP therapy due to high pressures and mask problems, the change from CPAP to BPAP has the potential to improve adherence to treatment and symptoms significantly. In the studied cohort, the prevalence of morbid obesity, OHS, diabetes and hypertension were high. Objectively, both treatment modalities, CPAP and BPAP, can achieve good nocturnal respiratory control during domiciliary therapy. However, to achieve long-term symptomatic benefit satisfactory treatment adherence is essential. The use of BPAP allowed for a reduction in the expiratory positive airway pressures needed to control OSA. More patients used BPAP therapy for longer periods than CPAP and this improved their symptom scores. Even in patients who had isolated OSA without any other type of SDB (50% of the cohort), symptoms (ESS) and respiratory control were improved with better adherence to BPAP. Uncontrolled symptoms, high pressures, mask problems and adverse treatment effects were the most common limiting factors for CPAP usage in our cohort. Interface related problems were reduced when patients used BPAP and did not impact adherence to the same extent as with CPAP.

CPAP is the first line therapy for moderate-severe OSA but second line alternatives such as mandibular advancement devices (MAD) for mild OSA, BPAP for moderate-severe OSA (with significant comorbidity) and, experimentally, the use of electrical stimulation need to be considered when first line therapy is not successfully employed [12] to address specific features of the phenotypically different OSA patients. [21] Previous studies have shown that BPAP and CPAP therapy can achieve similar efficacy in controlling OSA [17,22] but these studies did not focus on patients requiring high pressures to achieve control of OSA. A meta-analysis by Patil et

al, 2019 [18] found no clinically significant difference between CPAP and BPAP. The quality of the evidence used was low due to bias and imprecision and the majority of included trials studied a treatment naïve cohort of patients and did not select patients with high pressure requirements. [22-25] Furthermore, standard BPAP was only used in one study included. [25] Ballard et al, 2007 [26] included participants who had previously shown non-adherence to CPAP (<4hours/night) and reported an increase in adherence of 0.8 hours/night when patients used flexible BPAP (BiFlex). These results suggest a potentially beneficial use of BPAP as a second-line therapy for patients who are non-adherent to CPAP. [18] Recently, a study by Benjafield et al, 2019 [27] described that non-compliant patients with OSA on CPAP therapy could improve their adherence to treatment when changing to BPAP by 0.9hours/night. However, this was a retrospective data analysis of a cohort, without reporting specific demographics or symptomatic benefit of the patients. Consistent with their findings, our data indicated a relevant improvement in adherence to treatment on BPAP but further adds specific patient details and symptomatic outcomes (ESS). Unlike our study, Ballard et al 2017 [26] and Benjafield et al 2019 [27] did not select a cohort of patients requiring high CPAP pressures which may explain why we were able to improve adherence by a greater margin.

Patients with higher CPAP pressures are more likely to experience side effects, significant air leakage, disturbing sounds, discomfort and mask problems. However, there are sparse data on thresholds that would define what is a high CPAP level. CPAP inflates the chest and increases the functional residual capacity (FRC). The generated pressure impacts on the operational levels of the pressure volume curve, [28] offsets any intrinsic positive end-expiratory airway pressure (PEEPi) in supine posture [28,29], reduces the inspiratory effort and lowers neural respiratory

drive. [13,30] Higher pressures lead to a more forceful chest inflation and when patients are driven with their operational volumes (FRC) above the optimal level of chest inflation, then expiratory muscle activity is observed. [30] Our group has shown in CPAP titration studies of awake patients with OSA that higher CPAP is associated with discomfort and breathlessness. [30] In this study, patients developed symptoms associated with expiratory muscle activation at CPAP higher than 14cmH_2O, we therefore decided to define a high-pressure level as CPAP of 15cmH_2O and above.

Long-term treatment adherence for CPAP therapy can be limited despite the use of improved technology and behavioural interventions. [20] The use of lower expiratory pressures may improve comfort [30] and reduce mask leak. Tailoring ventilator settings by titrating IPAP, EPAP, adjusting flow triggers, Ti and mandatory backup breaths, as well as selecting the ventilator mode (volume/pressure-support/control) can replicate a physiological breathing pattern that reduces the inspiratory effort and positively impacts on respiratory muscle unloading. [31] Furthermore, patients with significant respiratory comorbidity that leads to hypercapnic respiratory failure may require the use of BPAP as the treatment of choice. BPAP yields better symptomatic improvements and can normalise hypercapnic respiratory failure [32,33] thus enhancing patient perception which impacts on long-term motivation for therapy. [34]

The question arises whether the significant changes in the adherence to treatment can make a difference to the clinical presentation. Although there is no hard evidence for a clearly established cutoff of CPAP usage time, it is typically accepted in clinical practice that >4hours/night defines an acceptable adherence to CPAP. A Cochrane review on behavioural interventions to improve CPAP adherence found that, overall, these interventions could improve usage by 0.59(95%CI 0.26-0.92)hours/night, [35] which is lower than the improvement in

adherence observed in our study. However, these data were largely derived from treatment of naïve patients and the authors stressed that it would be important to better understand the population of patients who previously struggled with CPAP adherence.

In order to assess clinical benefit, it is important to look at the symptomatic improvements. The minimal clinical important difference (MCID) for the ESS has recently been described by different groups as two or more points, [36,37] and patients on BPAP in our study improved by a larger margin. Recent studies also confirm that blood pressure control is more likely to benefit with CPAP usage >4h/night, [38] while higher CPAP pressures can also lead to detrimental effects on blood pressure while awake.[39]

We found significant improvements in treatment adherence with BPAP that were significantly larger than achieved by using educational, supportive or behavioural interventions; the improved adherence also led to reductions in the ESS above the MCID [36,37]. Optimisation of BPAP therapy to avoid patient-ventilator asynchrony is complex, even in a specialist setting. [22,40,41]

The current cohort represents a selected group of patients with a variety of comorbidities, including other causes of sleep disordered breathing. In particular, patients who had presented with OHS should have been directed to services establishing BPAP therapy in the first instance, this may have confounded our results and could explain why previous studies failed to show a difference in adherence. However, patients with OHS were in chronic and compensated hypercapnic respiratory failure, particularly when asleep, while the daytime blood gas analysis did not indicate any significant level of hypercapnia. Furthermore, this study was not a randomized controlled trial and, ideally, future studies should include well-designed trials focused on patients with isolated OSA. Additional data could be provided by repeat sleep study

(AHI) and BMI measurements. Furthermore, there is a risk of selection bias due to the time intervals between patients entering the BPAP referral pathway and initiation on therapy, although this reflects clinical practice. CPAP optimisation was trialed in all patients prior to the referral to BPAP. On CPAP therapy, 11 patients experienced difficulties with the mask, while 4 stated that they felt limited in the usage by claustrophobia. BPAP therapy improved adherence but did not entirely offset any problems; there were still 6 patients with limited adherence due to interface issues. However, claustrophobia, as reported on the high CPAP pressures, did not seem to be an issue any longer.

In conclusion, BPAP can be successfully employed in a cohort of obese patients with moderate-severe OSA who have limited adherence to CPAP due to high pressures and mask problems as longer adherence improves subjective sleepiness. Treatment-associated costs do not automatically justify the use of BPAP as a first line therapy despite its efficacy and the indication to use BPAP should be limited to specialist centres to identify eligible patients.

Data availability statement:

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Table 1 – The prevalence of co-morbidities in the studied cohort of patients with OSA (%).

Comorbidity	Patients affected (%)
Diabetes Mellitus (type II)	56
Respiratory	48
Hypertension	38
Neurological	25
Cardiovascular	17

∗**Table 1:** Respiratory co-morbidities included; asthma (4 patients), bronchiectasis (1 patient), chronic respiratory failure (6 patients), COPD (10 patients), cough syncope (1 patient), emphysema (1 patient), lung cancer (1 patient), mixed sleep apnoea (4 patients), obesity hypoventilation syndrome (17 patients),persistent pleural effusion (1 patients) and primary pulmonary hypertension (1 patient). Neurological co-morbidities included; benign intracranial hypertension (1 patient), Charcot-Marie-Tooth disease (1 patient), delayed sleep phase syndrome (1 patient), motor axonal neuropathy Guillain-Barré syndrome variant (1 patient), myotonic dystrophy (1 patient), narcolepsy with cataplexy (1 patient), paralysed hemi-diaphragm (3 patients), post-polio syndrome (1 patient) and restless leg syndrome (1 patient). Cardiac co-morbidities included; atrial fibrillation (2 patients), cardiomyopathy, dilated cardiomyopathy (1 patient), heart failure (3 patients), ischaemic heart disease (1 patient), mitral regurgitation (1 patient) and tachycardia (1 patient).

Table 2 - The reasons reported for sub-optimal CPAP adherence by the studied cohort of patients.

Reasons for sub-optimal CPAP therapy adherence	Number of patients reporting reason (% of total cohort)
High pressures	12 (23%)
Subjectively reported uncontrolled symptoms	12 (23%)
Mask problems	11 (21%)
Adverse effects	7 (13%)
Claustrophobia	4 (8%)
Co-morbidities	4 (8%)
Forgetting to put the mask on	1 (2%)
Other clinical interventions	1 (2%)

∗**Table 2**: The reasons stated by patients for sub-optimal CPAP adherence and the number of patients reporting each reason as well as the percentage of the total cohort this represents. Patients were asked to select only the main reason for problems, other specific concerns were then discussed in more detail. Co-morbidities included obesity hypoventilation syndrome and COPD.